THE CYCLIC CHANGES IN THE MAMMALIAN OVARY.

By LEO LOEB.

(*Read April 22, 1911.*)

The observations which I wish to report to you are of interest from several points of view:

1. The process upon which the sexual cycle in mammals depend has been analyzed, and a regulatory mechanism was found to exist within the ovary.

2. A striking illustration is presented of the fact that the structure of organs is in many instances at least not a definite one, but varies in correspondence with the functional condition of the organ.

3. The accurate description of the normal cyclic changes in the mammalian ovary serves as a basis for the investigation of the pathological deviations which interfere with the natural course of the sexual functions and may lead to a temporary or lasting sterility.

4. We found in the ovary structures which must in all probability be interpreted as early stages of embryos developing spontaneously parthenogenetically within the ovary and it is probable that the development of these parthenogenetic embryos is related to certain phases of the sexual cycle.

In the ovary of the guinea-pig definite and very interesting cyclic changes exist which I made the object of my studies in the last few years.

The mammalian ovary consists of two principal constituent parts, namely: First, large and small bodies lined by granulosa cells and filled with fluid, the so-called follicles; and, secondly, the corpora lutea. Both follicles and corpora lutea have only a brief existence; they develop to a certain point and then they degenerate and gradually disappear. The follicles contain the ova. At certain periods of the sexual cycle a few follicles that have reached maturity rupture. The ova reach the Fallopian tubes and uterus and after fertilization by a spermatozoön form an embryo in the uterine wall. New follicles situated in the periphery of the ovary grow constantly to a certain size and then degeneration sets in. The lining granulosa cells disintegrate and connective tissue grows into the cavity of the follicle. The ova in these degenerating follicles undergo frequently maturation and a few more or less regular divisions and then die. While thus the majority of follicles degenerate, become atretic, before they have reached maturity, a few follicles undergo certain progressive changes and become mature. They may rupture and discharge the ovum; such a rupture is called an ovulation. The process connected with ovulation causes a degeneration of all with exception of the smallest follicles. These follicles grow and in the course of the next six days they have reached that size at which degeneration may set in. We find, therefore, degenerating follicles from the seventh day after ovulation up to the time of the following ovulation. While after the seventh day medium-sized follicles constantly degenerate, new follicles grow and take the place of the degenerating disappearing ones. It seems that it takes approximately ten days until some of the follicles reach their full size.

We may therefore distinguish two periods in the ovarian cycle: First, the period of growth extending over the first seven days following ovulation, and, secondly, the period of equilibrium in which new follicles take the place of degenerating ones. After the first large follicles have appeared, it takes a few days longer until large follicles become transformed into mature follicles that are ready to rupture. We find, therefore, the first mature follicles to appear approximately eleven to thirteen days after ovulation and it would be natural to expect that about fourteen days after the preceding a new ovulation should take place.

The sexual period—that is the period between two ovulations—should therefore have a natural duration of approximately two weeks in the guinea-pig. This is, however, not the case. The sexual period in this species actually lasts about twenty to twenty-five days. And this is due to the fact that a mechanism exists within the ovary that prolongs the sexual cycle. In order to understand this mechanism, we must follow the fate of the ruptured follicle. A follicle that has ruptured at the time of ovulation does not degenerate in a similar manner as the other follicles do after they have reached full size, but they grow in a remarkable manner and form a new gland-like organ, the corpora lutea. Now these corpora lutea also degenerate after a period of growth that lasts approximately seventeen to twenty days. In the corpora lutea resides the mechanism that prevents a new ovulation. It is necessary that they degenerate before a new rupture of follicles can take place. As long as they function they prevent ovulation. The fact that the corpora lutea degenerate when seventeen to twenty days old, explains why a new ovulation takes place approximately every three weeks. If we excise the corpora lutea at an early date after ovulation, a new ovulation occurs very soon after mature follicles have made their appearance, approximately thirteen to fifteen days after the preceding ovulation. Under these conditions, the normal sexual cycle is reëstablished.

During pregnancy the life of the corpus luteum is prolonged in consequence of the changes occurring in the uterus or developing embryo during the period of gestation and in consequence of the prolonged life of the corpus luteum, a new ovulation is prevented during the whole course of pregnancy. Toward the latter part of pregnancy, the corpora lutea again degenerate and directly after completed labor a new ovulation can take place.

Ovulation, therefore, depends upon three factors: First, upon the maturation of ovarian follicles; secondly, upon the time of degeneration of the corpora lutea; and, thirdly, upon less important, more or less accidental conditions, as for instance, the process of copulation. The third class of conditions accelerates in many (not in all) cases ovulation, but it is not necessary for its occurrence. Even without a preceding copulation, ovulation usually takes place, but in many cases at a later date. Through what mechanism does the life of the corpus luteum influence ovulation? It might be conceivable that the corpus luteum delays the maturation of follicles thus preventing a rupture. My observations have, however, shown that an inhibiting influence of the corpus luteum upon the maturation of follicles does not exist. Mature follicles appear frequently during the life of the corpus luteum, and especially during the period of pregnancy; it seems that pregnancy even favors the maturation of follicles. The corpus luteum prevents, however, the *rupture* of the mature follicles. Pregnancy as such does not prevent the rupture provided the corpus luteum has been previously removed through excision.

The structural changes in the ovaries are rhythmical and so regular that a careful histological examination of these organs enables us to decide within a certain limit of accuracy at what period of the sexual cycle the animal had been at the time of the removal of the ovaries.

Having established the normal cycle I turned more recently my attention to its pathological deviations. It occurs in a certain number of animals—and I have observed this to happen among females which showed no desire for copulation or in which notwithstanding an accomplished copulation an ovulation did not follow—that the follicles do not grow to maturity, but that they undergo involution before they reach their full size, and that all, or almost all the follicles, become sclerosed, atretic, at a very early stage of their development. Under these conditions, an ovulation is impossible and the animal, in the ovaries of which such a deviation from the normal cyclic changes exists, are at least temporarily sterile; whether such a pathological condition may ever lead to a permanent sterility, future investigations must show. It will be readily understood that here we have to deal with questions of the greatest importance to the physiology of the sexual functions.

In order to appreciate thoroughly the conditions under which such abnormalities in the sexual cycle occur, it is necessary to produce the subnormal development of the follicles experimentally. Now it is of interest to know that such a premature involution of the ovarian follicles can be produced experimentally by burning a certain relatively small part of the ovaries with the thermocautery. The remaining larger part of the ovary remains apparently perfectly well, the cells functionate but the energy of growth of certain cells is diminished and subinvolution of the follicles with resulting temporary sterility follows. A comparable condition can be produced in tumors through heating, or through the influence of certain chemicals exerted in vitro as I found a number of years ago. Under such conditions the tumors grow, but with markedly diminished energy. In both cases, in the case of the tumors as well as of the ovaries, we have to deal with a state of living matter intermediate between its full natural vigor and latent life; we may regard it a state of partial shock of cells, in which the growth takes place but with a considerable decrease in energy. Besides the changes which I have just described, additional processes of the greatest interest take place in the ovaries of a certain number of animals and it is very probable that these processes usually commence at the period following ovulation and are therefore, in a certain sense, a part of the cyclic ovarian changes. The process I refer to concerns an apparently spontaneous partial parthenogenetic development of ova in the mammalian ovary, an occurrence of which I obtained convincing proof only within the last few months.

Some years ago I described peculiar structures that are found in the ovaries of guinea-pigs, and I expressed the opinion that they originated in the ovarian follicles.[1] Very soon after I had published my observations, certain considerations suggested to me that these structures owe their origin to parthenogenetically developing ova.

In as much as at that time I had not yet seen early stages of the structures referred to, I was unable to regard this hypothesis as sufficiently founded to warrant publication. I continued, however, my investigations in this direction, and recently I succeeded in finding in two animals the desired early stages. They must be interpreted as embryos developing parthenogenetically within the ovary of the guinea-pig. We see in each case a chorionic vesicle with trophoblast, and plasmodia and syncytia penetrating into the neighboring tissues. There is present also a structure which is probably to be interpreted as a neural tube.

Aberrant blastomeres (remnants of dividing ova that failed to participate in the embryonic development) cannot be seen in the ovaries of guinea-pigs, and, inasmuch as the embryonic structures, described in my former communication, are relatively frequent, occurring in approximately ten per cent. of all guinea-pigs below the age of six months, and, furthermore, inasmuch as they are situated

[1] *Archiv f. mikrosk. Anatomie*. Bd. 65, 1905.

in the cortex of the ovaries at a place where follicles lie normally and are found within follicle-like cavities, they can only be derived from ova developing parthenogenetically. Fertilization through spermatozoa can be excluded, inasmuch as the history of some of these animals is known to us and precludes such an interpretation. It is very probable that the parthenogenetic development sets in soon after ovulation, the altered conditions in the ovaries at that time (variations in blood pressure, in intrafollicular pressure or changes in gas exchange) supplying the necessary stimulus. This interpretation agrees well with my former observations concerning the parallelism existing between the first segmentations taking place in non-fertilized ova within the ovary and certain stages of atresia of follicles.[2]

It is also of interest to note that frequently these changes are multiple, several ova undergoing parthenogenetic development in the same ovary.

We may, therefore, conclude that in at least ten per cent. of all guinea-pigs parthenogenetic development of the ova within the ovary starts at some period of the life of the animal. The later stages of these developing embryos bear some resemblance to chorionepitheliomata, certain tumor-like formations consisting of proliferating chorion tissue. During ovulation these structures are occasionally injured by hemorrhages and they are ultimately invaded and supplanted by the neighboring connective tissues.

These observations throw furthermore light on certain interesting tumors that are especially found in the ovaries and testicles, namely: the teratoid tumors and the chorionepitheliomata. My observations are a strong argument in favor of the view that teratoid tumors that are found in the ovaries are not derived from misplaced blastomeres, as Bonnet and Marchand believed, but that the older view is correct according to which they are derived from parthenogenetically developed ova, an opinion which I, also, expressed on previous occasions. The same statement can be made in the case of the chorionepitheliomata that occur in the ovaries and in the testicles. I believe that the observations here recorded clear up the mechanism of the sexual

[2] "On Progressive Changes in the Ova in Mammalian Ovaries," *Journal of Medical Research*, Vol. 1, 1901.

cycle in its essential aspects and they also make it extremely probable that in a relative large proportion of mammalian animals a spontaneous parthenogenetic development of ova takes place at some period during the life of the animal.

Department of Pathology,
Barnard Free Skin and Cancer Hospital,
St. Louis, Missouri.